Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	September 23, 2015
Reviewer:	Miriam Chehab, PharmD, Safety Evaluator Division of Pharmacovigilance II
Acting Team Leader:	Samantha Cotter, PharmD, BCPS, FISMP Acting Safety Evaluator Team Leader Division of Pharmacovigilance II
Deputy Division Director:	S. Christopher Jones, PharmD, MPH, MS Deputy Division Director Division of Pharmacovigilance II
Product Name:	Implanon, Nexplanon, Liletta, Mirena, Skyla, and ParaGard
Subject:	Cases of Death
Application Type/Number:	NDA 021529, NDA 021225, NDA 203159, NDA 206229, and NDA 018680
Applicant/Sponsor:	Multiple
OSE RCM #:	2015-2121

1 INTRODUCTION

The Division of Bone, Reproductive, and Urologic Products (DBRUP) consulted the Division of Pharmacovigilance II (DPV-II) via e-mail on September 21, 2015 to review the FDA Adverse Event Reporting System (FAERS) for reports of death with the long-acting reversible contraceptive products (implants or intrauterine systems). The specific products include Implanon (etonogestrel implant), Nexplanon (etonogestrel implant), Liletta (levonorgestrel-releasing intrauterine system), Mirena (levonorgestrel-releasing intrauterine system), Skyla (levonorgestrel-releasing intrauterine system), and ParaGard T 380A (intrauterine copper contraceptive).

This high-level summary was requested on behalf of the Center for Devices and Radiological Health (CDRH) in preparation for the September 24, 2015 Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee Meeting.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Cases were included if the outcome of death was documented.

Cases were excluded if the case described:

- An elective termination of pregnancy
- An ectopic pregnancy without maternal death

2.2 FAERS SEARCH STRATEGY

DPV searched the FDA Adverse Event Reporting System (FAERS) with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	September 21, 2015
Time Period of Search	November 15, 1984† - September 21, 2015
Search Type	Quick Query
Product Terms	Product Name: Implanon, Nexplanon, Liletta, Mirena, Skyla, ParaGard T 380A
MedDRA Search Terms (Version 18.0)	All adverse events
Other Search Criteria	NDA Number: 021529, NDA021529, 021225, NDA021225, 203159, 206229, 018680 Outcome: Death U.S. Cases
* See Appendix A for a description of the FAERS database. † FDA approval date of ParaGard. Implanon, Nexplanon, Liletta, Mirena, and Skyla were all FDA approved after	

Table 1. FAERS Search Strategy*
this date.

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 92 total U.S. reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, 74 cases were included in the case series of death reported with Implanon, Nexplanon, Liletta, Mirena, Skyla, or ParaGard (see Figure 1).

A hands-on analysis of these cases has not been performed; therefore, cases have not been assessed for causality or a temporal relationship.

Figure 1. FAERS Case Selection

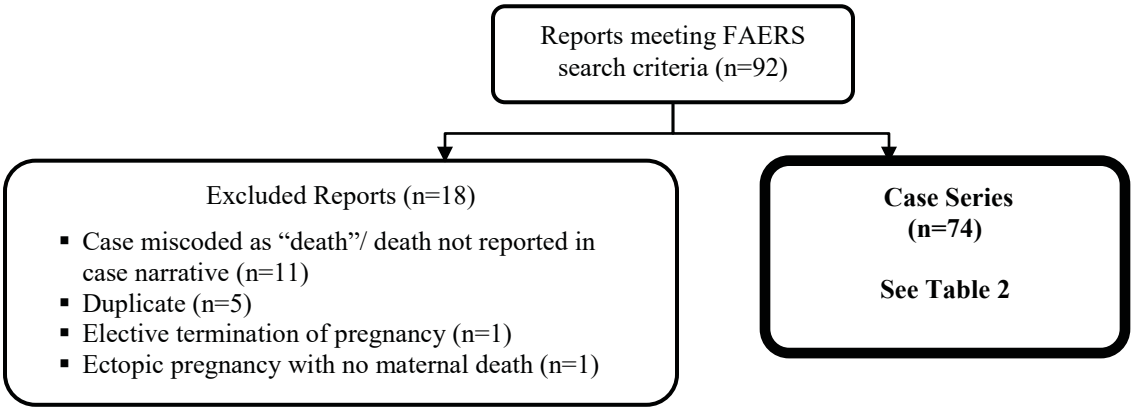

Table 2 summarizes the 74 total FAERS cases of death reported with Implanon, Nexplanon, Liletta, Mirena, Skyla, or ParaGard. Appendix B lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 74 cases in this case series.

Table 2. Descriptive Characteristics of U.S. FAERS Cases of Death Reported with Implanon, Nexplanon, Liletta, Mirena, Skyla, or ParaGard Received by FDA from November 15, 1984, to September 21, 2015 (n=74)*†

Age (years) (n=36)	Mean	21.7
	Median	25.5
	Range	0 - 50
Sex‡	Female	45
	Male	6
	Unknown/Not reported	23
Report Type	Expedited	61
	Direct	7
	Periodic	6
Product	Mirena§	49
	Implanon	14

Table 2. Descriptive Characteristics of U.S. FAERS Cases of Death Reported with Implanon, Nexplanon, Liletta, Mirena, Skyla, or ParaGard Received by FDA from November 15, 1984, to September 21, 2015 (n=74)*†		
	ParaGard	7
	Nexplanon	4
	Liletta	0
	Skyla	0
Events Reported^	Miscarriage/Stillbirth/Fetal Demise	21
	Death of premature infant post-delivery	16
	Adult death (not otherwise specified)	10
	Infant death (not otherwise specified)	5
	Sepsis	4
	Thromboembolic event	4
	Infection	3
	Malignancy	3
	Seizure	3
	Cardiac arrest/Myocardial infarction	2
	Cerebral infarction/Cerebrovascular accident	2
	Suicide	2
	Autoimmune disorder	1
	Hemorrhage	1
	Intestinal perforation	1
	Motor vehicle accident	1
	Ruptured ectopic pregnancy	1

* Cases were not assessed for causality or a temporal relationship.
† Fetal and infant cases that were reported with an outcome of death were included in this case series. Fetal cases were composed of miscarriages, stillbirths, and fetal demise. For the purposes of this review, an infant is defined as age < 1 years old.
‡ Fetal and infant cases are included in this cases series.
§ 17 of the 49 Mirena cases were litigation reports.
^ An individual case may contain more than one event.

4 REVIEWER'S COMMENTS

DPV-II identified FAERS cases of death reported with Implanon, Nexplanon, Mirena, and ParaGard. No cases of death were identified with Liletta or Skyla. It is important to note that these cases were not reviewed to assess a causal association or a temporal relationship, and without careful evaluation, there is no certainty that a reported event was actually due to the product.

Comparison between the different long-acting reversible contraceptive products should not be made because of multiple factors, including the difference in drug availability based on FDA approval, variability in drug usage, and the potential for stimulated reporting of certain products.

In addition, it is important to be aware of the following limitations of FAERS data:

- Underreporting is a known limitation of FAERS. Drug manufacturers are required to notify FDA when they become aware of adverse events associated with their products; however, many events are never reported to the manufacturer, and therefore, never reported to the Agency. FDA also voluntarily receives reports of adverse events from health care professionals and consumers; however, we only receive reports for a small proportion of the events that actually occur. Because of underreporting, FAERS data cannot be used to estimate the incidence of an event, and this data should not be used to compare the relative risk of an event among a group of products. Furthermore, FAERS data cannot be used to estimate the safety risk of an event compared to a known background rate, as in the case of miscarriage, stillbirth, fetal demise, and premature delivery, for which study data is usually needed for further risk assessment.

- The reporting of an event does not prove a drug-event association. Determining causation from a case report alone can be difficult, even for rare or unusual events.

- Data quality in spontaneous reporting systems, such as FAERS, can be highly variable, and present a challenge upon interpretation.

The predominant strength of FAERS is to detect rare adverse events associated with drug and biologic products that were not identified during pre-approval clinical trials. An outcome of death that is potentially attributed to a product is better studied using more robust methods, such as observational or randomized controlled studies.

Little can be inferred from the data that DPV-II has provided in this document, other than FDA has received reports coded with an outcome of death with some of the long-acting reversible contraceptives. The nature of this association is unknown.

5 APPENDICIES

5.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

5.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

Product Name	FAERS Case #	FAERS Version #	Manufacturer Control #
Mirena	6657527	1	Direct Report
	6838903	3	US-BAYER-200839950NA
	6879349	2	US-BAYER-200910421NA
	6902859	1	Direct Report
	7241308	1	Direct Report
	7248064	3	US-BAYER-201011051NA
	7547910	1	US-BAYER-201027621NA
	7547919	3	US-BAYER-201029543NA
	7836392	1	US-BAYER-2011-016590
	7836396	1	US-BAYER-2011-016592
	7838339	1	US-BAYER-2011-016591
	7960626	1	US-BAYER-2011-042269
	7972620	1	US-BAYER-2010-002095
	7979538□	1	US-BAYER-2011-046657
	8275973□	1	US-BAYER-2011-114989
	8694315□	1	US-BAYER-2012-073668
	8736906□	2	US-BAYER-2012-084784
	8763387□	3	US-BAYER-2012-087176
	8765741□	1	US-BAYER-2012-089059
	9026627□	1	Direct Report

Product Name	FAERS Case #	FAERS Version #	Manufacturer Control #
	9061323	3	US-BAYER-2013-013445
	9113330	1	US-BAYER-2013-014954
	9311187	3	US-BAYER-2013-064523
	9385414	1	US-BAYER-2013-079794
	9438209	2	US-BAYER-2013-093430
	9472366	1	US-BAYER-2013-101861
	9645939	3	US-BAYER-2013-128572
	9726313	1	US-BAYER-2013-145070
	9748851	3	US-BAYER-2013-150369
	9801014	5	US-BAYER-2013-158759
	9871018	1	US-BAYER-2014-016201
	10044375	1	US-BAYER-2014-047052
	10046937	1	US-BAYER-2014-047084
	10057091	1	US-BAYER-2014-047046
	10086157	1	Direct Report
	10141869	1	US-BAYER-2014-060420
	10189095	2	US-BAYER-2014-075314
	10191951	1	US-BAYER-2014-075320
	10215837	2	US-BAYER-2014-083114
	10391184	1	US-BAYER-2014-120164
	10547854	1	US-BAYER-2014-154392
	10609710	1	US-BAYER-2014-171840
	10716394	1	US-BAYER-2015-006026
	10879513	1	US-BAYER-2015-030541
	10995103	1	US-BAYER-2015-091087
	11222719	1	US-BAYER-2015-360385
	11380168	1	US-BAYER-2015-394114
	11444879	1	US-BAYER-2015-409274
	11496985	1	US-BAYER-2015-416430
Implanon	6946224	1	2009-192590-NL
	7006073	1	2009-196526-NL
	7065960	1	2009-200527-NL
	7269887	2	2010SP003303
	7857608	2	2011SP006656
	8140187	1	2011SP039687
	8457730	2	2012SP010583
	8670101	2	2012SP035989
	8738499	3	US-009507513-1208USA007211
	8799523	1	Direct Report
	9243069	1	US-009507513-1304USA009264
	9312777	3	US-009507513-1305USA013948
	9451671	3	US-009507513-1308USA004058
	9530431	2	US-009507513-1309USA006491

Product Name	FAERS Case #	FAERS Version #	Manufacturer Control #
ParaGard	3356072□	1	PRIUSA1999006065
	3462334□	1	PRIUSA2000004067
	3729237□	1	NSADSS2001032164
	3949698□	3	NSADSS2003022599
	6055348□	2	FEI2006-0685
	8349065□	1	306880USA
	10971270□	1	Direct Report
Nexplanon	9448270	2	US-009507513-1308USA000234
	10170879	3	US-009507513-1405USA004262
	10312846	2	US-009507513-1407USA007095
	11495321	2	US-009507513-1509USA002429

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/s/

MIRIAM M CHEHAB
09/23/2015

SAMANTHA A COTTER
09/23/2015

STEVEN C JONES
09/23/2015